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Synthesis of Unusual α-Amino Acids *via* a 2+2+2 Cycloaddition Strategy [1]

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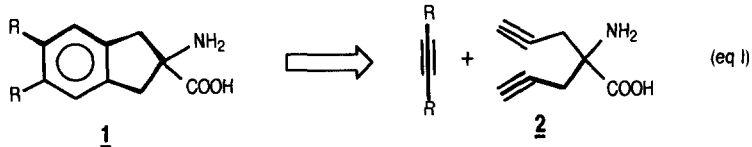
Abstract: A simple method for the preparation of diyne building block **5** and its use in the synthesis of indane-based α-amino acid derivatives *via* a 2+2+2 cycloaddition strategy is reported.

Conformationally constrained α-amino acids (AAAs) play an important role in peptide design. [2] Only simplest members of AAAs are ordinarily used because general methods for their synthesis have not been available. The documented difficulties involved with the most commonly used Bucherer-Berg method for the syntheses of cyclic AAAs has encouraged us to search for alternative methods.[3] In this regard, we sought a process which is not restricted to a simple substitution pattern and also would be sufficiently flexible to generate various derivatives of unusual AAAs. Our approach is based on the development of new building blocks embodying AAA moiety which are useful in the preparation of diverse AAAs. The motivation for these investigations was the expectation that new advances in the preparation of such building blocks might allow the syntheses of complex AAAs. In this communication we wish to report a simple preparation of diyne building block **5** and its use in the preparation of indane-based AAAs *via* a 2+2+2 cycloaddition strategy.



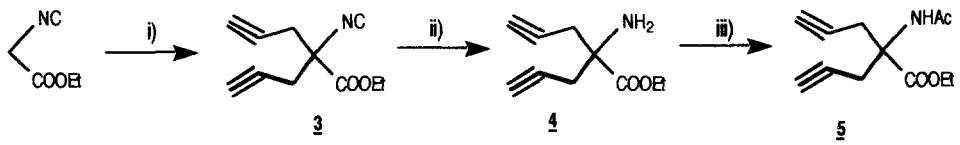
(eq I)

1 **2**

A simple retrosynthetic analysis of **1** (eq I) *via* three-bond disconnective approach identifies diyne **2** and monoyne as the possible synthons. Cycloaddition approach to AAAs is strategically different from the other known routes.[3] The present route involves generation of benzene ring *via* a 2+2+2 cycloaddition reaction, while the other methods are based upon manipulation of pre-formed benzene derivatives. Since cycloaddition reactions can create considerable functionality in the final target molecule by judicious selection of participants, this strategy may be convenient for the introduction of diverse functionality in **1**.

Our initial efforts to prepare the diyne building block **3** *via* propargylation of benzylidene derivative of glycine ethyl ester under phase-transfer catalyst (PTC) conditions were unsuccessful. We selected PTC conditions because of our long term objective of developing enantioselective synthesis of AAAs using chiral PTCs. After screening several glycine anion equivalents,[4] we found that commercially available ethyl isocyanoacetate [5] was suitable for our purpose. Thus, compound **3** was prepared in 80% yield (Scheme 1) under PTC(tetrabutylammonium hydrogen sulfate) conditions in refluxing acetonitrile/K_2CO_3. [6] The structure of **3** was established on the basis of complementary spectral data. [7]

Scheme 1



3 **4** **5**

i) propargyl bromide, K_2CO_3, CH_3CN, Bu_4NHSO_4 ii) 1 N HCl iii) Ac_2O, ultrasound

After acquisition of **3**, the next task in our hand is to attempt 2+2+2 cotrimerization reaction. The 2+2+2 cycloaddition of acetylene to give benzene has been found to be a symmetry allowed and very exothermic reaction (ΔH = -142 kcal/mole). However due to kinetic factors, the reaction does not readily take, requiring excess reaction temperature or a suitable catalysts. Recently, Grigg and co-workers reported Wilkinson's catalyst (WC) is useful for inter- and intramolecular 2+2+2 cycloaddition reactions to generate indane derivatives.[8] Because of simplicity of this procedure we choose WC as our first choice.

While the inherent reactivity of isonitrile group towards hydrolysis was advantageous for the generation of amino functionality, its lability under cycloaddition conditions led us the preparation of N-acetyl derivative **5**.[7] Thus, hydrolysis of **3** with few drops of con. hydrochloric acid gave amino ester **4** which was protected using acetic anhydride under sonication conditions to deliver compound **5** (m.p. 116-118^{0}C) in 88% isolated yield (**3** to **5**). The nine line ^{13}C NMR spectrum exhibiting resonances at δ 170.7, 169.9, 78.4, 71.4, 62.5, 61.7, 25.1, 23.7, 14.1 provided an unequivocal evidence that C_2 symmetry had been maintained during the acetylation step.

Initially, we attempted cotrimerization reaction using diyne **5** and dimethyl acetylene-dicarboxylate (DMAD)(1 equivalent) in ethanol at reflux temperature using WC conditions and found that starting material was recovered. Grigg and coworkers reported [8] that some of the side reactions are often effectively suppressed by adding excess amount of monoyne. When the cotrimerization reaction was carried out with excess of DMAD no required product was formed.

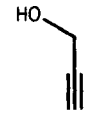
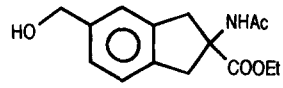
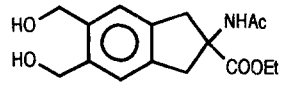
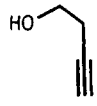
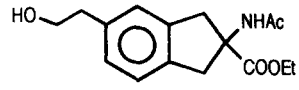
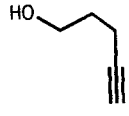
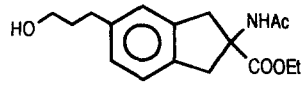
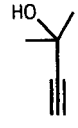
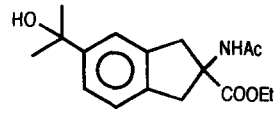
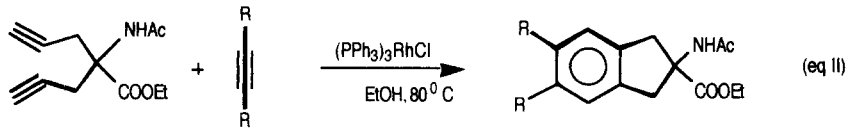
Entry No.	Monoyne	Product	Yield
1		 **6**	81%
2		 **7**	68%
3			97%
4			50%
5			95%

Table 1



(eq II)

5

Later on, the cotrimerization was perfomed with excess amount of propargyl alcohol, the required product **6** (m.p., 136-137 ^{0} C) was formed in 81% isolated yield. Various AAA derivatives prepared using this cycloaddition approach (eq II) are shown in Table 1. We are currently evaluating other catalysts to prepare several unusual AAA derivatives containing interesting functionalities.

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7. Spectral data: Compound **3**: ^{13} C NMR ($CDCl_3$, 75.4 MHz), δ 165.87, 161.6, 75.82, 73.41, 64.51, 63.44, 28.23, 13.89. Compound **6**: ^{13} C NMR ($CDCl_3$, 75.4 MHz), δ 172.96, 170.32, 140.43,140.06, 139.44, 126.15, 124.69, 123.50, 66.10, 65.27, 61.77, 43.45, 43.27, 23.15, 14.17. Compound: **7** (m.p. 122-124 ^{0}C), ^{13} C NMR ($CDCl_3$, 75.4 MHz), δ 173.14, 170.92, 140.16, 138.51, 125.80, 66.01, 63.65, 61.80, 43.14, 22.67, 14.16.

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